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(54) Title: PHARMACEUTICAL PREPARATIONS FOR EXTERNAL USE CONTAINING NON-STEROIDAL ANTI-INFLAMMATORY AND ANALGESIC AGENTS

(57) Abstract

The present invention relates to an anti-inflammatory and analgesic pharmaceutical preparation for external use having excellent percutaneous absorption and applicability. The pharmaceutical preparations for external use of this invention comprise NSAIDs and as a percutaneous absorption promoting agent oleic acid or oleyl alcohol in a pharmaceutically acceptable aqueous alcoholic solvent.

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Pharmaceutical Preparations for External Use Containing Non-Steroidal Anti-inflammatory and Analgesic Agents

Field of the Invention

This invention relates to an anti-inflammatory and analgesic pharmaceutical preparation for external use having excellent percutaneous absorption and applicability.

Background of the Invention and Prior Art

Non-steroidal anti-inflammatory and analgesic agents have an excellent anti-inflammatory and analgesic activity and have been widely used in clinical field in the dosage form of pharmaceutical preparations for external use such as ointments, gel ointments, creams, lotions or sticking plasters, oral pharmaceutical preparations such as capsules or the like, suppositioies or injections.

It has been hitherto common that non-steroidal anti-inflammatory and analgesic agents (hereinafter referred to as NSAIDs) have been orally administered in the dosage form of capsules, tablets, etc. Although they when orally administered can show an excellent effect, they exhibit considerable side effects on absorption from the gastrointestinal tracts and, therefore, should be carefully handled in actual application. Accordingly, with an object of reducing the side effects such as gastrointestinal disorders by topical application for external use, there have been developed those techniques, for example, gels (Japanese Patent Kokai Application No. 161323/1981), creams (Japanese Patent Kokai Application Nos. 103811/1983 and 298526/1987), ointments (Japanese Patent Kokai Application No. 39616/1983), sticking plasters (Japanese Patent Kokai Application No. 250317/1989) and others. However, even in these inventions, there have remained the problems that, because of poor diffusion and transfer of the NSAIDs in a base phase of the sticking plasters, release of the drug is insufficient and that percutaneous absorption from ointments (gel bases) is not so good as expected.

Problems to be Solved by the Invention

Accordingly, it is an object of this invention to provide a cutaneous pharmaceutical preparation for external use wherein the percutaneous absorption of the NSAIDs is improved.

Means to Solve the Problems

Under such circumstances, the present inventors have made intensive studies and, as a result, have found that the percutaneous absorption of an NSAID is significantly improved by adding at least one percutaneous absorption promoting agent selected from the group consisting of oleic acid and oleyl alcohol to a specific water-soluble base.

More specifically, this invention relates to a pharmaceutical preparation for external use which comprises the NSAIDs and as a percutaneous absorption promoting agent oleic acid or oleyl alcohol in a pharmaceutically acceptable aqueous alcoholic solvent.

Mode for Carrying Out the Invention

As the aqueous alcoholic solvent which may be employed in this invention, there may be preferably mentioned a homogeneous mixed solvent of a polyhydric alcohol selected from the group consisting of a monohydric saturated aliphatic alcohol of 1-4 carbon atoms, a saturated aliphatic glycol of 2-4 carbon atoms and glycerol and water.

As the monohydric saturated aliphatic alcohol, there may be mentioned methanol, ethanol, n-propanol, isopropanol and the like, and ethanol and isopropanol may be particularly preferable.

As the saturated aliphatic glycol, there may be mentioned ethylene glycol, propylene glycol, 1,3-butylene glycol, isopropylene glycol (3-methyl-1,3-butanediol) and the like.

As the polyhydric alcohol, there may be mentioned said glycol and/or glycerol, and glycerol is particularly preferable.

A preferable blended proportion of such aqueous alcoholic solvent is 15-70% by weight, more preferably 30-65% by weight, for the monohydric saturated alcohol, 0.1-30% by weight, more preferably 0.5-15% by weight, for the polyhydric alcohol and 10-60% by weight, more preferably 20-50% by weight, for water. When the proportion of the monohydric saturated aliphatic alcohol is too low, solubility of the NSAIDs is lowered whereby turbidity appears and stability is lowered. The polyhydric alcohol, more preferably glycerol, may be preferably used at 5-30% by weight to the said monohydric saturated alcohol while satisfying said blended proportion.

It is essential in this invention to combine such specified aqueous alcoholic solvent with oleic acid and/or oleyl alcohol. These percutaneous absorption promoting agents may be used alone or in combination.

Oleic acid is preferred and cis-oleic acid is most preferred. A blended proportion of such percutaneous absorption promoting agents is 0.1-15% by weight based upon a total weight of the preparation for external use and, particularly, 0.5-10% by weight is preferable. If it is too small, a promoting effect on percutaneous absorption could not be accomplished.

Above about 15% promoting agent, further improvement in the absorption of the NASAID is not significant.

The active ingredient NSAIDs may be blended preferably at 0.1-10% by weight, particularly preferably at 0.5-5% by weight based upon a total weight of the preparation for external use.

It is preferable for the anti-inflammatory and analgesic preparation for external use to further incorporate therein menthol, especially 1-menthol. A blended proportion of menthol may be 0.5-5% by weight based upon a total weight of the preparation for external use.

The anti-inflammatory and analgesic pharmaceutical preparation of this invention may be preferably applied in the dosage form of liquids or gels for utilizing this invention more effectively. These dosage forms may use conventional bases and blending components in compliance with the desired dosage form. As the water-soluble polymers which may be commonly used as a gelling agent may be mentioned, for example, carboxyvinyl polymer, carboxymethylcellulose sodium, polyvinyl alcohol, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, hydroxypropylmethylcellulose, etc. such a gelling agent may be applied at 0.1-5% by weight based upon a total weight of the preparation for external use.

Also, there may be optionally added humectants, antiseptics, antioxidants, coloring agents, perfumes, thickening agents, etc., if required, to the anti-inflammatory and analgesic pharmaceutical preparation of this invention.

Effect of the Invention

In accordance with this invention, there is provided a cutaneous pharmaceutical preparation for external use of the NSAIDs having an excellent percutaneous absorption property. Significantly, the dermatologic pharmaceutical preparation for external use of the NSAIDs having an excellent percutaneous absorption property can reduce side effects such as gastrointestinal, hepatic and renal disorders caused by continued oral administration and shows no pain which is a disadvantage in the case of invections and, therefore, a potent therapeutic effect can be expected to chronic articular rheumatish, peritendinitis, muscle pain, swelling and pain after woulds, etc.

Percutaneous absorption effect, pharmacological effect and stimulation to the skin by the anti-inflammatory and analgesic pharmaceutical preparation for external use according to this invention will be explained in greater detail by way of the following examples.

Examples

The following formulated preparations were prepared by Examples 1-4 and Comparative Examples 1 and 2 according to a conventional method, while commercially available ketophenol-containing dermatologic drugs for external use were used in Comparative Examples 3-5.

Example 1

Lotions	
Ethanol	56% by weight
Ketoprofen	3% by weight
1-Menthol	3% by weight
Oleic Acid	0.8% by weight
Oleyl Alcohol	4.2% by weight
Glycerol	6% by weight
Water	27% by weight

Example 2

Lotions	
Isopropanol	56% by weight
Ketoprofen	3% by weight
1-Menthol	3% by weight
Oleic Acid	0.8% by weight
Oleyl Alcohol	4.2% by weight
Glycerol	6% by weight
Water	27% by weight

Example 3

Lotions	
Ethanol	50% by weight
Ketoprofen	3% by weight
1-Menthol	3% by weight
Oleic Acid	4% by weight
Glycerol	6% by weight
Water	34% by weight

Example 4

Gels	
Ethanol	56% by weight
Ketoprofen	3% by weight
1-Menthol	3% by weight
Oleic Acid	0.8% by weight
Oleyl Alcohol	0.2% by weight
Glycerol	5.7% by weight
Hydroxypropylcellulose	0.5% by weight
Diisopropanolamine	0.4% by weight
Water	29.8% by weight

Example 5

Lotions	
Ethanol	56% by weight
Indomethacin	1% by weight
1-Menthol	3% by weight
Oleic Acid	0.8% by weight
Oleyl Alcohol	4.2% by weight
Glycerol	6% by weight
Water	27% by weight

Example 6

Lotions	
Isopropanol	56% by weight
Bufexamac	1% by weight
1-Menthol	3% by weight
Oleic Acid	0.8% by weight
Oleyl Alcohol	4.2% by weight
Glycerol	6% by weight
Water	27% by weight

Example 7

Gels	
Ethanol	56.6% by weight
Ibuprofen	2% by weight
1-Menthol	3% by weight
Oleic Acid	0.8% by weight
Oleyl Alcohol	0.2% by weight
Glycerol	5.7% by weight
Hydroxypropylcellulose	0.5% by weight
Diisopropanolamine	0.4% by weight
Water	29.8% by weight

Comparative Example 1

Lotions	
Ethanol	56% by weight
Ketoprofen	3% by weight
1-Menthol	3% by weight
Glycerol	6% by weight
Water	32% by weight

Comparative Example 2

Lotions	
Ethanol	71% by weight
Ketoprofen	3% by weight
1-Menthol	3% by weight
Oleic Acid	1% by weight
Oleyl Alcohol	4% by weight
Glycerol	18% by weight

Comparative Example 3 Lotions

Epatec A Lotion (Zeria-Nissan Chemical)

Comparative Example 4

Epatec A Gel (Zeria-Nissan Chemical)

Comparative Example 5 Indomethacin-containing gels

Vantelin Kowa Gel (Kowa)

Comparative Example 6 Lotions

Lotions	
Ethanol	56% by weight
Indomethacin	1% by weight
1-Menthol	3% by weight
Oleic Acid	0.8% by weight
Oleyl Alcohol	4.2% by weight
Glycerol	6% by weight
Water	32% by weight

Comparative Example 7 Lotions

Lotions	
Isopropanol	56% by weight
Bufexamac	1% by weight
1-Menthol	3% by weight
Glycerol	6% by weight
Water	34% by weight

Comparative Example 8 Lotions

Lotions	
Ethanol	71% by weight
Bufexamac	1% by weight
1-Menthol	3% by weight
Oleic Acid	1% by weight
Oleyl Alcohol	4% by weight
Glycerol	18% by weight

Test Examples for Evaluation

The NSAIDs containing pharmaceutical preparations made by Examples and Comparative Examples were tested for the evaluation of their percutaneous absorption effect, pharmacological effect and stimulation to skin.

Test Example 1 Test on skin permeability **in vitro**

Hartley strain male guinea pigs 4 weeks of age were anesthetized with Nembutal by intraperitoneal injection and the hair on the back of the animals was clipped by hair clipper and then the skin was collected. Subcutaneous tissues were removed as much as possible from the collected skin without damaging the epidermis and the skin was cut into skin sheets of about 2 cm square. The sheets were placed in a diffusion cell of a Franz type having an effective diffusion area of 0.785 cm^2 . The diffusion cell was kept at 37°C by a circulating water of constant temperature and the side of receptor of the cell was filled with 5 ml of an aqueous solution containing 5% of bovine serum albumin for receiving ketoprofen which was sparingly soluble in water. The skin was applied to the diffusion cell and allowed to stand for 2 hours until the system reached a stationary state and then 1 ml of a test solution was placed

on the donor side of the cell. In order to prevent evaporation of the solution from the donor side, it was tightly sealed with parafilm. Thereafter, 100 μl each of the aqueous solutions at the receptor side was sampled with lapse of time. Acetonitrile (500 μl) was added to the collected sample to precipitate and remove the bovine serum albumin and the liberated ketoprofen was determined by a conventional method using HPLC. The measurement parameters for the HPLC were as defined below:

Column (for ketoprofen); STR ODS-II(I.D.4.6mm x L. 15 cm): Mobile phase; acetonitrile:100mM phosphate buffer=4:6 : Flow rate; 1 ml/min.: Column temperature; 25°C:Detection; 254nm.

Column (for indomethacin); STR ODS-II(I.D.4.6mm x L. 15 cm): Mobile phase; acetonitrile:10mM phosphate buffer=4:6 : Flow rate; 10 ml/min.: Column temperature; 25°C:Detection; 254nm.

Column (for bufexamac); STR ODS-II(I.D.4.6mm x L. 15 cm): Mobile phase; 2.5g of sodium 1-octanesulfonate and 0.6g of sodium ethylenetetraacetate were dissolved in 800 ml of water and to the solution were added 500ml of methanol, 500ml of acetonitrile and 8ml of glacial acetic acid : Flow rate; 1.0ml/min.: Column temperature; 25°C:Detection; 254nm.

Accumulated amounts of the NSAIDS which permeated through the skin to the receptor side after 12 hours from the initiation of the test are shown in Table 1.

Table 1

Accumulated rate permeated through the skin

Ketoprofen 3%	Permeated amount through the skin ($\mu g/cm^2$)
Example 1	812
Example 2	910
Example 3	775
Comparative Example 1	35
Comparative Example 2	158
Comparative Example 3	258

Indomethacin 1%	Permeated amount through the skin ($\mu g/cm^2$)
Example 5	320
Comparative Example 6	19
Comparative Example 5	91

Bufexamac 1%	Permeated amount through the skin ($\mu g/cm^2$)
Example 6	279
Comparative Example 3	21

Comparative Example 8

In the case of ketoprofen, lotions obtained by Examples 1-3 showed a better percutaneous absorption than that of lotion obtained by Comparative Example 1 containing neither oleic acid nor oleyl alcohol, lotion obtained by Comparative Example 2 containing no water and a competitive lotion product used in Comparative Example 3. Similar results were obtained in both cases of indomethacin and bufexamac. It is apparent from the above results that the anti-inflammatory and analgesic preparation for external use according to this invention can significantly promote the percutaneous absorption of the NSAIDs.

Test Example 2 Test on pharmacological effect

2-1 Test on inhibition of edema induced by carrageenin

Anti-inflammatory action of the anti-inflammatory and analgesic preparation for external use according to this invention (Example 4) and that tof competitive preparations from another company (Comparative Examples 4 and 5) were evaluated by a test on inhibition of carrageenin-induced edema. Volume of right hind paw of rats of Wistar strain (male; eight weeks of age) was measured using a paw volume measuring device (MK-550; manufactured by Muromachi Kikai K.K.) and then the rats were divided into five groups (each group consisting of eight rats) so that the mean value of paw volumes in each of the group became approximately equal. Each preparation (50mg) was applied to the area around the site of right hind paw to which carrageenin is to be administered and, after 2 hours, the same amount was applied again to the same area. After 0.5 hours from the second application, the applied drug

was removed using a gauge which was wetted with warm pure water and 0.08 ml of 1% carrageenin was subcutaneously administered immediately. After 2, 3 and 4 hours from the administration of carrageenin, paw volumes were measured and the swelling rate was calculated from the difference between the paw volumes before and after application of the preparation. Incidentally, after application of the preparation, the administered site was covered with a wrapping film (Salan Wrap; manufactured by Asahi Chemical Industries Co., Ltd.) and an expandable adhesive tape (Silky Tex; manufactured by ALCARE) was applied thereon to fix, so that the rats were no longer able to take the preparation orally. In control group, the same operations were conducted except for the application of the preparation.

Test results are shown in Fig. 1. The preparation of Example 4 significantly inhibited the edema induced by subcutaneous administration of carrageenin from 2 to 4 hours since the induction. The swelling rate was lower than those of Comparative Examples 4 and 5 until 4 hours from the induction. The swelling rate of Example 4 at 4 hours from the induction was 14.8% (the inhibition rate to the control group was 70.2%) which was the lowest while the swelling rate (and the inhibiting rate in the same sense as above) of Comparative Examples 4 and 5 were 25.4% (47.7%) and 35.6% (26.7%), respectively.

2-2 Test on pain reaction of inflammatory paw induced by yeast
(Randall and Selitto method)

Analgesic action of the anti-inflammatory and analgesic preparation for external use according to this invention (Example 4) and of competent products of another company (Comparative Examples 4 and 5) were evaluated by a test on pain reaction of inflammatory paw induced by yeast. Thus, 0.1 ml of a 20% yeast suspension was subcutaneously administered to right hind paw of Wistar strain (male; 5 weeks of age) so that inflammation was induced. After 2 hours, the pain threshold value of the inflammatory paw was measured using a threshold value measuring device of a compression type (MK-800; manufactured by Muromachi Kikai K.K.). Among the animals used, those wherein the pain threshold of the yeast-induced inflammatory paw was not more than 50% of the value before the infuction were selected and were divided into five groups (each group consisting of eight rats) so as

to make the mean value of the pain threshold value in each group approximately equal. Each preparation (50mg) was applied around the site where the yeast was administered and the pain threshold value of theinflammatory paw after 1, 2, 4 and 8 hours from the administration was measured. Incidently, after application of the preparation, the administered site was covered with a wrapping film and an expandable adhesive tape was applied thereon to fix, so that the rats were no longer able to take the preparation orally. In control groups, the same operations were conducted except for the application of the preparation. The test results are shown in Figure 2.

As compared with the control group, the preparation of Example 4 significantly raised the pain threshold value, which had been lowered by subcutaneous administration of yeast, during the 1 to 6 hour period following its application. The pain threshold value after one hour from the application showed the highest value (69.4g) and maintained the values of about 1.7-2.2-fold of those of the control until 6 hours. Comparative Examples 4 and 5 similarly raised the threshold values significantly until 6 hours, but the pain threshold values after one hour from the application were 51.9 and 65.6g for Comparative Examples 4 and 5, respectively, which were lower than the data by Example 4.

From the above results of the pharmacological tests, application of the product according to this invention to the inflammatory site showed quicker onset of the effect as compared with other anti-inflammatory and analgesic preparations and, additionally, the pharmaceutical effect was very good, while maintaining for 4 or 6 hours after application.

Test Example 3 Evaluation of safety by application to human being

Safety of the anti-inflammatory and analgesic preparation for external use according to this invention (Example 4) and the competitive products of another company (Comparative Examples 4 and 5) in human healthy skin was investigated by an open patch test and a closed patch test by a closed sticking for 24 hours. The test was conducted by 18 healthy male adults (age: 20-24, 21.8 in average) and 18

females (age: 20-45; 25.8 in average). In an open patch test, a circle with 1 cm diamater was frawn on inner side of the upper arm of the persons to be tested, a preparation was uniformly applied within the circle using an applicator in accordance with a previously-fixed allotting table of the preparations and then determination was made after 20 minutes, 24 hours and 48 hours. In a closed patch test, a sample was permeated into a filter paper placed on a fin chamber and subjected to a closed adhesion to inner side of the upper arm using a Scanpor tap for 24 hours in accordance with a previously-fixed allotting table. Judgement was made after 60 minutes and also 24 hours from the removal of the sample. Both judgements were conducted in accordance with the standard regulated by the Patch Test Study Association of Japan as mentioned below.

Criteria for judgement according to the
Patch Test Study Association of Japan

No reaction----------; (-)
Slight red spots ----------; (ı)
Apparent red spots ----------; (+)
Red spots + Swelling----------; (+ +)
Red spots + Swelling + Papules or Vesicles ----------; (+ + +)
Big vesicles ----------; (+ + + +)

In the case where apparent allergy reaction was noted, the corresponding score was marked with a circle.

Results of the adhesion test are shown in Table 2 (open patch test) and in Table 3 (closed patch test). In the open patch test, no reaction was noted on the skin in any of the preparations tested. In the closed patch test, one case of apparent red spots (+) was noted in Comparative Example 5 in the judgement of after 60 minutes from the removal and, in the judgement of after 24 hours from the removal, each one case of apparent red spots (+) was noted in Examples 4 and 5, while, in Example 4, only slight red spots (±) were noted. Table 3 shows stimulation indexes calculated from the results of the closed patch test. From this result, it is apparent that the

preparations of Examples 4 and 5 are included within a category of allowable products. From the above, it can be concluded that the preparations of Examples 4 and 5 are a product having no problem in actual use, because, in the open patch test which is close to the situation of actual use, no positive reaction was noted at all while, in the closed patch test using a fin chamber, stimulation is apt to occur as compared with the actual use but the degree of the stimulation is similar to or less than that of the commercially available preparations.

Table 2 Open patch test

Judging time	Judgement in 20 minutes after application			Judgement in 24 hours after application			Judgement in 48 hours after application		
Positive rating / Sample	≧++	≧+	≧±	≧++	≧+	≧±	≧++	≧+	≧±
Example 4	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %
Example 5	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %
Comparative Example 4	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %
Comparative Example 5	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %	0/36 0 %

Table 3 Closed patch test

Judging time	Judgement in 60 minutes after removal			Judgement in 24 hours after removal		
Positive rating / Sample	≧++	≧+	≧±	≧++	≧+	≧±
Example 4	0/36 0 %	0/36 0 %	3/36 8.3%	0/36 0 %	0/36 0 %	3/36 8.3%
Example 5	0/36 0 %	0/36 0 %	5/36 13.9%	0/36 0 %	1/36 2.8%	5/36 13.9%
Comparative Example 4	0/36 0 %	0/36 0 %	4/36 11.1%	0/36 0 %	1/36 2.8%	1/36 2.8%
Comparative Example 5	0/36 0 %	1/36 2.8%	11/36 30.6%	0/36 0 %	1/36 2.8%	12/36 33.3%

Table 4 Stimulation Indexes

Judging time / Sample	60 minutes after removal	24 hours after removal
Example 4	4.2	4.2
Example 5	6.9	9.7
Comparative Example 4	5.6	4.2
Comparative Example 5	18.1	19.4

WHAT IS CLAIMED

1. An anti-inflammatory and analgesic pharmaceutical preparation for external use which comprises a non-steroidal anti-inflammatory and analgesic agent and a percutaneous absorption promoting agent selected from oleic acid and oleyl alcohol in a pharmaceutically acceptable aqueous alcoholic solvent.

2. The anti-inflammatory and analgesic pharmaceutical preparation for external use as claimed in Claim 1 wherein said pharmaceutically acceptable aqueous alcoholic solvent is composed of a polyhydric alcohol selected from the group consisting of a monohydric saturated aliphatic alcohol of 1-4 carbon atoms, a saturated aliphatic glycol of 2-4 carbon atoms and glycerol and water.

3. The anti-inflammatory and analgesic pharmaceutical preparation for external use as claimed in Claim 1 or 2 wherein it further contains menthol.

4. The anti-inflammatory and analgesic pharmaceutical preparation for external use as claimed in any of Claims 1-3 wherein it further contains a gelling agent.

5. The anti-inflammatory and analgesic pharmaceutical preparation for external use as claimed in any of Claims 1-4 wherein it contains said non-steroidal anti-inflammatory and analgesic agent at 0.1-10% by weight based upon a total weight of said pharmaceutical preparation for external use.

6. The anti-inflammatory and analgesic pharmaceutical preparation for external use as claimed in any of Claims 1-4 wherein it contains said percutaneous absorption promoting agent at 0.1 –15% by weight based upon a total weight of said pharmaceutical preparation for external use.

7. The anti-inflammatory and analgesic pharmaceutical preparation for external use as claimed in any of Claims 2-6 wherein it contains said monohydric saturated aliphatic alcohol at 15-70% by weight, said polyhydric alcohol at 0.1-30% by weight and water at 10-60% based upon a total weight of said pharmaceutical preparation for external use.

8. The anti-inflammatory and analgesic pharmaceutical preparation for external use as claimed in any of Claims 3-7 wherein said mentol is l-menthol and is contained at 0.5-5% by weight based upon a total weight of said pharmaceutical preparation for external use.

9. The anti-inflammatory and analgesic pharmaceutical preparation for external use as claimed in any of Claims 2-8 wherein said monohydric saturated aliphatic alcohol is selected from the group consisting of ethanol and isopropanol.

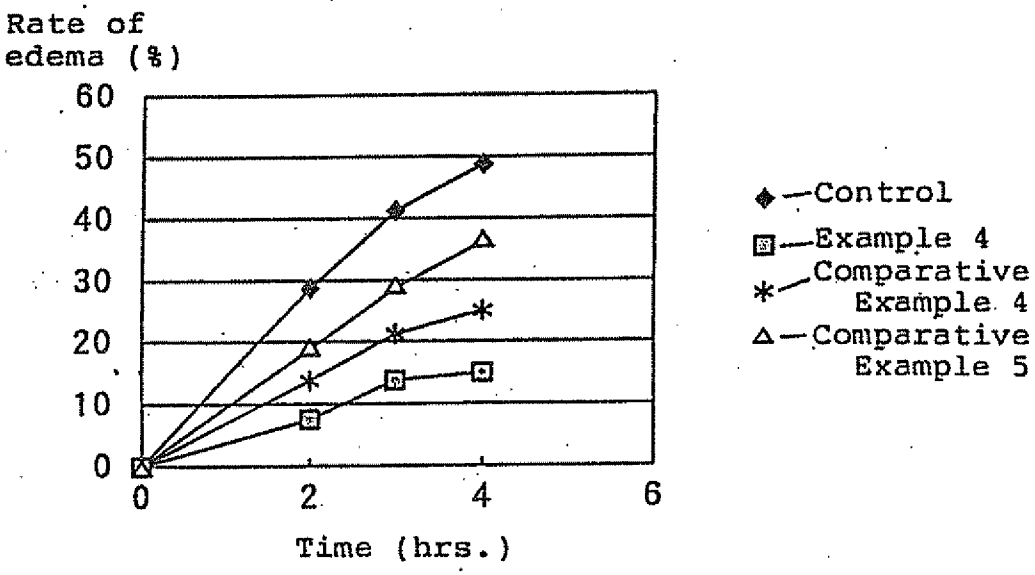
10. The anti-inflammatory and analgesic pharmaceutical preparation for external use as claimed in any of Claims 2-9 wherein said polyhydric alcohol is glycerol.

11. The anti-inflammatory and analgesic pharmaceutical preparation for external use as claimed in any of Claims 2-9 wherein it contains said gelling agent at 0.1-5% by weight based upon a total weight of said pharmaceutical preparation for external use.

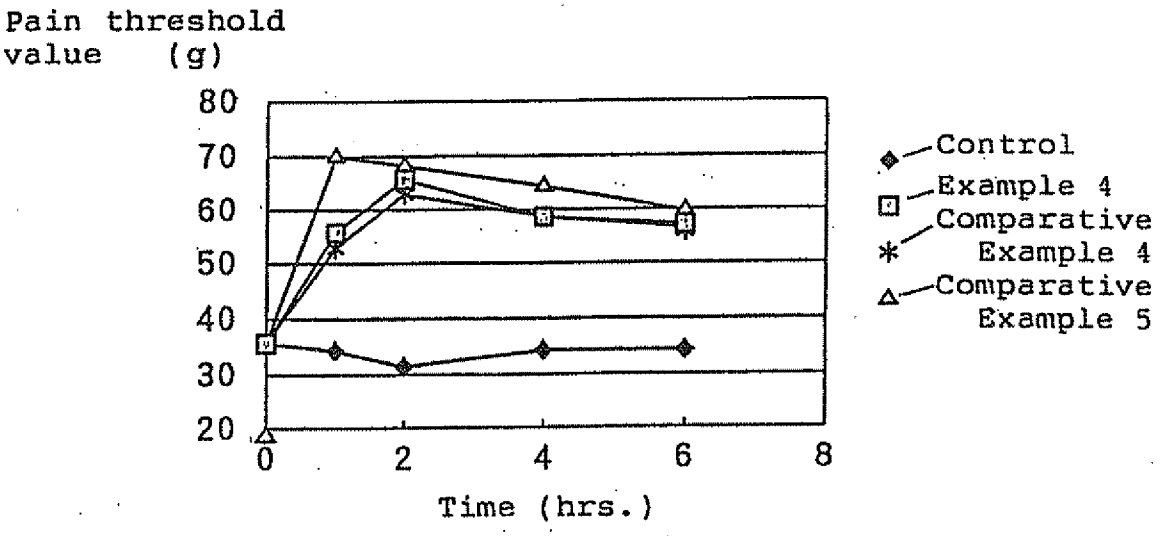
12. The anti-inflammatory and analgesic pharmaceutical preparation for external use as claimed in any of Claims 1-11 wherein said percutaneous absorption promoting agent is cis-oleic acid.

13. The anti-inflammatory and analgesic pharmaceutical preparation for external use as claimed in any of Claims 1-12 wherein said non-steroidal anti-inflammatory and analgesic agent is ketoprofen, indomethacin, bufexamac, ibuprofen or piroxicam.

[Fig. 1]


Rate of edema (%)
60
50
40
30
20
10
0
0
2
4
6
Time (hrs.)
Control
Example 4
Comparative Example 4
Comparative Example 5

[Fig. 2]


Pain threshold value (g)
80
70
60
50
40
30
20
0
2
4
6
8
Time (hrs.)
Control
Example 4
Comparative Example 4
Comparative Example 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/25555

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/70; A61K 9/6
US CL : 424/449; 514/947
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/449; 514/947

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST, USPATFUL: Non steroidal anti-inflammatory, NSAID, analgesic, topical, cutaneous, transdermal, penetration enhance, menthol, oleic acid, oleyl alcohol.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,827,886 A (HERSH) 27 October 1998, col. 8, lines 30-49; col. 17, lines 10-30; col. 18, lines 22-41.	1-3
Y	US 5,434,292 A (SAITA et al) 18 July 1995, col. 9, line 32 to col. 10, line 61; col. 36, lines 15-46.	1-3
Y	EP 0491076 A1 (THERATECH, INC.) 24 June 1992, see abstract; page 2, lines 18-36.	1-3

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
19 JANUARY 2000

Date of mailing of the international search report
16 FEB 2000

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/25555

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 4-13
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.